A Brief Report on Outcomes of Stereotactic Ablative Radiotherapy for a Second Primary Lung Cancer: Evidence in Support of Routine CT Surveillance

Gwendolyn H.M.J. Griffioen, MD, Frank J. Lagerwaard, MD, PhD, Cornelis J.A. Haasbeek, MD, PhD, Ben J. Slotman, MD, PhD, and Suresh Senan MRCP, FRCR, PhD

Abstract: New guidelines recommend the use of CT surveillance after a curative treatment for lung cancer as survivors have a 3–6% risk per person year of developing a second primary lung cancer. Our analysis of 107 patients with second primary lung cancer treated by stereotactic ablative radiotherapy showed a comparable 3 years overall survival (60%) and local control rate (89%) as for an initial lung cancer. Toxicity was uncommon, despite the fact that 73% of patients had undergone a prior (bi)lobectomy. Our findings indicate that CT surveillance is also appropriate in patients who may be unfit, or unwilling, to undergo surgery.

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After the curative treatment of a lung cancer, the risk of developing a second primary lung cancer (SPLC) ranges between 3% and 6% per person year.[1] Recent guidelines recommend follow-up of such patients by CT-scans for the detection of a treatable relapse or new primary tumors.[2,3] However, the role of routine CT surveillance in lung cancer survivors is controversial as no survival benefit has yet been demonstrated in patients with a recurrence and also because of concerns about the toxicity of curative therapies in this setting.[4]

Although many patients developing a SPLC may be candidates for a second resection,[5] a substantial proportion may be ineligible because of comorbidities or impaired lung function. Less fit patients with early-stage non–small-cell lung cancer (NSCLC) are eminently suitable for stereotactic ablative radiotherapy (SABR), a highly conformal hypofractionated radiotherapy technique, with low toxicity and actuarial local control rates at 3 years of more than 90%.[6] As there is limited literature on the outcomes of SABR for this indication,[7,8] our goal was to evaluate local control and toxicity for a SPLC treated with SABR at a single institution and to determine whether there could be a benefit of CT surveillance in the less fit patients presenting with a SPLC.

MATERIALS AND METHODS

Patients undergoing SABR for early-stage NSCLC at the VU University Medical Center are registered in a prospective institutional database. Between April 2003 and January 2013, 863 patients underwent SABR for stage I NSCLC. For this analysis, we identified patients with a prior history of lung cancer, in whom the minimum interval was 6 months between the diagnosis of the initial and second tumor, and the initial tumor was under control at time of diagnosis of the second tumor. A total of 107 patients with a metachronous SPLC were identified. Patients undergoing a pneumonectomy for the initial tumor followed by SABR for the SPLC have been the subject of an earlier publication,[9] but were not excluded from this analysis. Baseline patient and tumor characteristics of the initial and second lung cancer were collected, including treatment details. In accordance to the Medical Research Involving Human Subjects Act, The Netherlands, retrospective reviews are exempt from medical ethics review, and the informed consent of patients was not sought.

Patient selection criteria, and our SABR treatment protocol, have been described previously.[10,11] Briefly, staging was performed using FDG-PET-CT-scans, and all patients were discussed in a multidisciplinary tumor board. SABR was delivered to a biologically equivalent dose of ≥100 gray (Gy_{10}), prescribed in 3, 5, or 8 fractions, depending on T-stage and the proximity to the mediastinum or chest wall. Standardized follow-up took place at 3, 6, and 12 months and yearly thereafter.

Time to local, regional or distant failure was calculated from the start of SABR. Disease-free survival was defined as the time between the start of SABR and the occurrence of any failure. The treatment interval was defined as the time between the start of treatment for the initial tumor and that of SABR. Because of the limited data available on treating SPLC with SABR, we compared the outcomes of patients with SPLC with the outcomes of the 756 patients in our SABR database who were treated for a "first" primary lung cancer (FPLC; T1-2N0M0).

Department of Radiation Oncology, VU University Medical Center, Amsterdam, the Netherlands.

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Address for correspondence: Gwendolyn Griffioen, Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: g.griffioen@vumc.nl

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Toxicity was scored using the Common Toxicity Criteria for Adverse Events version 4.0. Toxicity reported within 3 months after SABR was labeled as "acute toxicity," and all toxicity reported after 3 months of SABR was labeled as "late toxicity". For all descriptive statistics and calculations, IBM SPSS version 20.0 was used. A p value less than 0.05 was considered statistically significant.

TABLE 1. Patient, Tumor, and Treatment Characteristics (n = 107)

Characteristics	n (%) or Median (Range)
Male gender	73 (68%)
Age at SPLC (years)	72 (50–90)
Treatment interval (months)	48 (6–349)
COPD	85 (79.4%)
Charlson Comorbidity Index	3 (0–10)
WHO Performance Score (PS)	1 (0–3)
Stage initial lung cancer (7th TNM)	
Stage I	67 (62.6%)
Stage II	18 (16.8%)
Stage III	17 (15.9%)
Stage IV	3 (2.8%)
Unknown	2 (1.9%)
Treatment initial lung cancer	
Lobectomy/bilobectomy/trimodality	78 (72.9%)
Pneumonectomy	17 (15.9%)
Wedge/segmentectomy	3 (2.8%)
CRT	7 (6.5%)
Palliative (chemo or RT)	2 (1.9%)
Histology initial lung cancer	
Squamous cell carcinoma	50 (46.7%)
Adenocarcinoma	39 (36.4%)
NSCLC	11 (10.3%)
SCLC	1 (0.9%)
Unknown	4 (3.7%)
Double tumor—different histology	2 (1.9%)
Histology SPLC	11 (10.2%)
Squamous cell carcinoma	10 (9.3%)
Adenocarcinoma	4 (3.7%)
NSCLC	82 (76.6%)
Unknown	
Histology initial lung cancer and SPLC	
Same	16 (15.0%)
Different	9 (8.4%)
Unknown	82 (76.6%)
Stage SPLC (7th TNM)	
T1aN0	41 (38.3%)
T1bN0	34 (31.8%)
T2aN0	28 (26.2%)
T2bN0	4 (3.7%)
Diameter SPLC (mm)	23 (9–69)
PTV SPLC (cc)	20.7 (4.4–135.5)
Fractionation scheme SPLC	5 (3–8)
Dose SPLC (Gy)	60 (54–60)

SPLC, second primary lung cancer; COPD, chronic Obstructive Pulmonary Disease; PTV, planning target volume; NSCLC, non–small-cell lung carcinoma; SCLC, small-cell lung carcinoma; CRT, chemo-radiation; chemo, chemotherapy; RT, radiotherapy; WHO, World Health Organization; TNM, tumor, node, metastasis.

RESULTS

Baseline patient, tumor and treatment characteristics are summarized in Table 1. Patients treated for SPLC were predominately male (68%) with a median age of 72 years and a median Charlson comorbidity index of 3 (non-age-adjusted; range: 0–10). Nearly all (98%) of the second lesions showed FDG-PET uptake, and the two remaining lesions had shown growth on consecutive chest CT-scans.

Six patients were treated with SABR for a third primary lung tumor, a single patient for a fourth. The initial primary tumor was predominately stage I-II (79.4%) according to the 7th tumor, nodes, metastasis (TNM) staging system, had squamous cell carcinoma histology (46.7%), and most of these had been treated by (bi)lobectomy (72.9%). The median interval between the treatment of the initial and second tumor was 48 months (range, 6–349). Histology of the SPLC was unknown in 76.6% and a multidisciplinary tumor board assessed the risk of malignancy to be high, in accordance with guidelines of the European Society for Medical Oncology.[2] For 25 patients in whom pathology was available for both lesions, 64% had the same histology.

The median follow-up duration after treatment of SPLC was 46 months, calculated by the reversed Kaplan-Meier method. The median overall survival (OS) was 39.9 months, with a 1- and 3-year OS of 86% and 60%, respectively (Fig. 1). The 3-year local, regional, and distant control rates were 89%, 91%, and 85%, respectively. The median disease-free survival was not reached and was 80% at 3 years. Twelve patients with a SPLC (11% of total) developed a third (or fourth) primary lung tumor at a median of 20 months after SABR (range, 7–36 months).

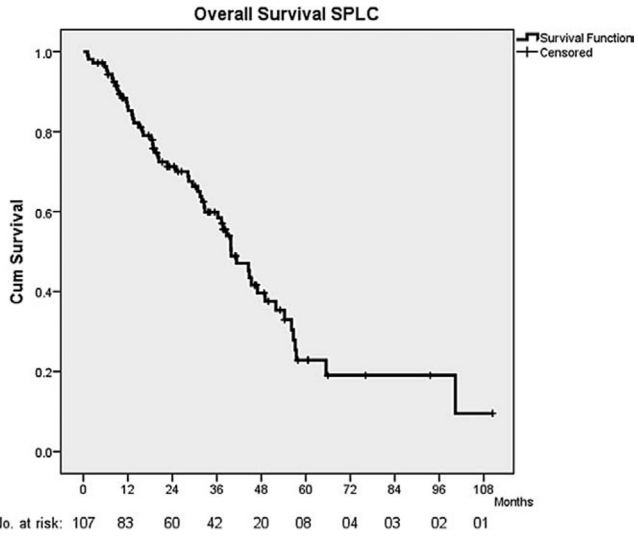

FIGURE 1. Kaplan-Meier curve for overall survival of patients treated with stereotactic ablative radiotherapy for metachronous second primary lung cancer (SPLC; n = 107).

Reported acute grade ≥3 toxicity included a single case of grade 3 brachial plexopathy at 2 months after SABR in a patient with a tumor located in the apex of the left lung. Acute radiation-induced pneumonitis necessitating steroids (grade 2) was observed in less than 1% of patients. Late radiation-induced pneumonitis necessitating steroids was noted in 7% of patients. In addition, late grade ≥3 toxicity was reported in 3.7% of patients and included one case of grade 3 hemoptysis, for which blood transfusion was required. A single patient experienced an embolism of the right pulmonary artery (grade 4), in conjunction with a regional nodal failure. Two cases of grade 5 toxicity were observed; one patient experienced a bleeding in a post-SABR cavitation with secondary infection by aspergillus; another patient experienced hemoptysis and respiratory failure associated with a bronchial stricture.

A comparison with patients treated in the same period with SABR for a FPLC (n = 756) is illustrated in Figure 2 and showed no significant differences with respect to OS (p = 0.73), local control (p = 0.24), regional control (p = 0.49) and distant control (p = 0.69).

DISCUSSION

Despite an estimated risk of 3–6% per person year of developing a SPLC, there is controversy regarding the use of routine CT scans after curative treatment of a primary lung cancer. There are concerns about the fitness of such patients to undergo a second curative therapy as decreases in quality of life after surgery are well recognized.[12] We studied the outcomes of a large cohort of patients with SPLC treated with SABR, an outpatient treatment involving up to eight high-dose fractions delivered with extremely high precision.

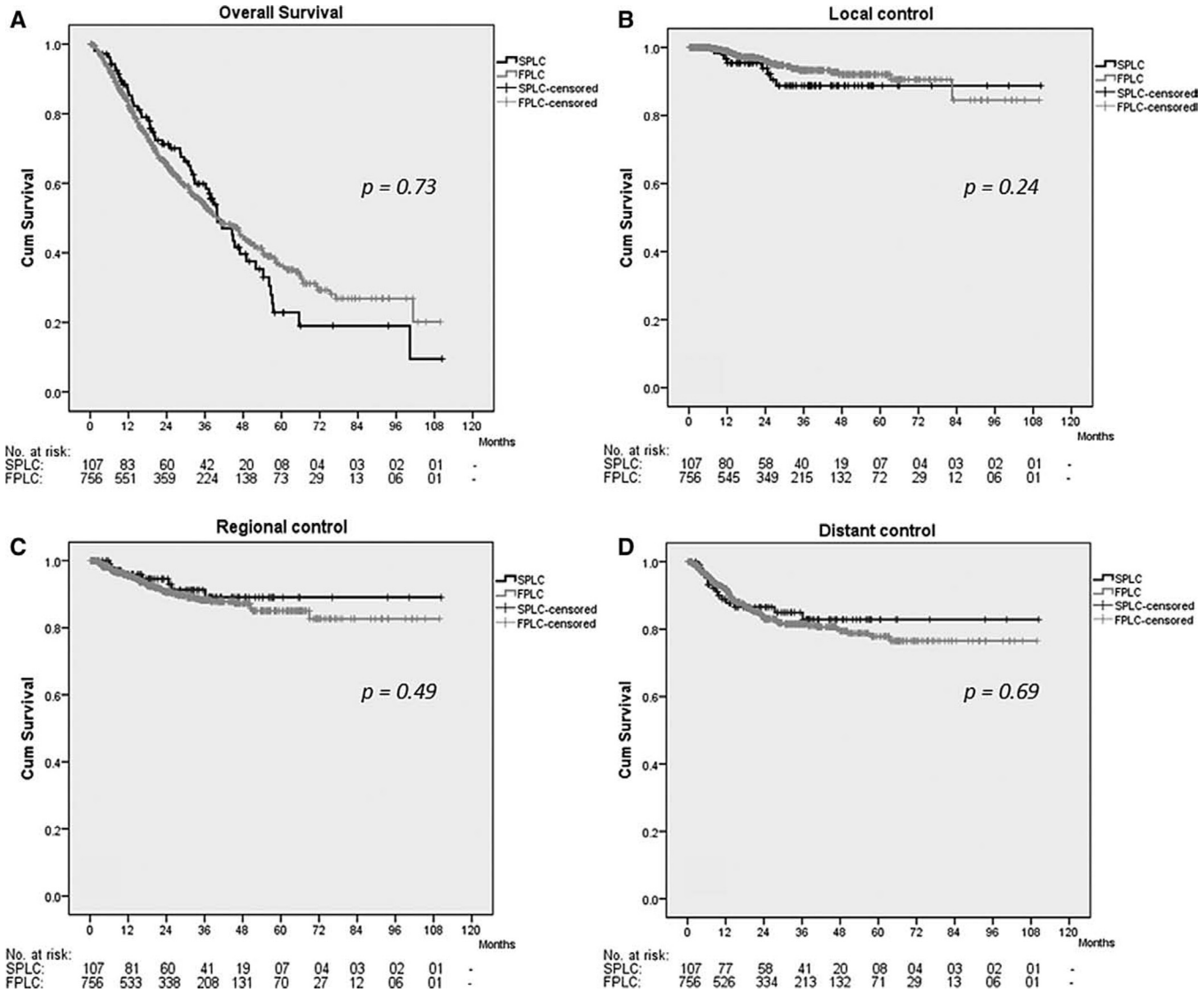

FIGURE 2. Kaplan-Meier curves comparing (*A*) overall survival and (*B*) local, (*C*) regional, and (*D*) distant control rates between patients treated with stereotactic ablative radiotherapy for a "first" primary lung cancer (FPLC; gray line, n = 756) and a metachronous second primary lung cancer (SPLC; black line, n = 107)

Our analysis revealed that the outcomes of SABR for SPLC are no different than for an initial presentation of an early-stage NSCLC, with a 3-year OS of 60% and local control rates of 89% at 3 years. Toxicity was uncommon despite a population with prior surgery.

Our findings support the current guidelines in North America and Europe recommending routine surveillance,[2,3] even in patients who may not be fit for further surgery. The observation that 11% of our patients developed a third (or fourth) primary lung cancer during follow-up after SABR emphasizes that lung cancer survivors remain at high risk for developing new primary lung tumors.

To the best of our knowledge, this is the largest series on SABR for SPLC. One publication on 62 SPLC patients reported a 4-year survival of 53%,[7] and another on 48 pts reported a 2-year survival of 68 %.[8] These data are broadly consistent with our findings.

A recent large surgical series of 161 cases of metachronous SPLC, reported a 5-year survival of 60% compared with 23% in our series.[13] However, OS is generally superior in surgical cohorts as eligibility for surgery implies having fewer comorbidities and better lung function. This is also illustrated by the difference in the number of patients with prior pneumonectomy in the surgical series (4.3%) compared with our cohort (15.9%).

One limitation of our analysis is the fact that a pathological diagnosis was not available in many cases of SPLC, which is in contrast to the situation before treatment of the initial lung cancer. However, previous work in the Dutch population has shown that the incidence of benign disease is low in surgical cases, after a multidisciplinary tumor board has made a clinical diagnosis of lung cancer.[14,15] Another concern might be that the treated lesion represented a solitary metastasis instead of SPLC. However, as the outcomes after SPLC are similar to outcomes after FPLC (Fig. 2), this is less likely. It could also have been argued that some of our patients were potentially operable, despite having undergone a previous anatomical resection. However, a growing body of data on SABR from high-risk populations suggests that SABR achieves comparable local control and OS as with surgery.[6] In conclusion, our findings indicate that CT surveillance is also appropriate in patients who may be unfit, or unwilling, to undergo surgery.

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